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# Randomized phase II trial of carboplatin versus paclitaxel and carboplatin in platinum-sensitive recurrent advanced ovarian carcinoma: a GEICO (Grupo Español de Investigación en Cáncer de Ovario) study

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**Background:** The aim of this study was to determine whether the response rate for the paclitaxel–carboplatin combination is superior to carboplatin alone in the treatment of patients with platinum-sensitive recurrent ovarian carcinoma.

**Patients and methods:** Patients with recurrent ovarian carcinoma, 6 months after treatment with a platinum-based regimen and with no more than two previous chemotherapy lines, were randomized to receive carboplatin area under the curve (AUC) 5 (arm A) or paclitaxel 175 mg/m$^2$ + carboplatin AUC 5 (arm B). The primary end point was objective response, following a 'pick up the winner' design. Secondary end points included time to progression (TTP), overall survival, tolerability and quality of life (QoL).

**Results:** Eighty-one patients were randomized and included in the intention-to-treat analysis. The response rate in arm B was 75.6% [26.8% complete response (CR) + 48.8% partial response (PR)] [95% confidence interval (CI) 59.7% to 87.6%] and 50% in arm A (20% CR + 30% PR) (95% CI 33.8% to 66.2%). No significant differences were observed in grade 3–4 hematological toxicity. Conversely, mucositis, myalgia/arthralgia and peripheral neurophaty were more frequent in arm B. Median TTP was 49.1 weeks in arm B (95% CI 36.9–61.3) and 33.7 weeks in arm A (95% CI 25.8–41.5). No significant differences were found in the QoL analysis.

**Conclusions:** Paclitaxel–carboplatin combination is a tolerable regimen with a higher response rate than carboplatin monotherapy in platinum-sensitive recurrent ovarian carcinoma.

**Key words:** combination chemotherapy, platinum sensitive, randomized clinical trial, recurrent ovarian carcinoma

## Introduction

Ovarian carcinoma is still the most common cause of death from gynecological cancer in the Western world. Despite high sensitivity to chemotherapy and with an objective response rate to first-line chemotherapy in advanced disease of 60% to 80%, the majority of patients will relapse and die from chemo-resistant disease. Thus, >80% of patients with advanced ovarian carcinoma will be considered for a second-line treatment at the time of disease recurrence [1]. Over the past 10 years, several new drugs have been shown to be active in second-line therapy. However, no randomized trials have shown any drug to be the best second-line option [2].

Patients who initially respond to platinum-based chemotherapy and maintain a relapse-free interval >6 months have a probability of response to a new platinum-based treatment of at least 30%, and are considered to have platinum-sensitive disease. As Markman et al. [3] demonstrated, those with a longer platinum-free interval, i.e. >24 months, reach a significantly higher response rate than patients with an interval

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<24 months (77% versus 28%; $P<0.001$). For those patients with a platinum-sensitive relapse, carboplatin has been the preferred option by the majority of oncologists because of its easy administration, favorable toxicity profile (no alopecia, limited nausea, manageable hematological toxicity) and recognized antitumor activity [4, 5]. All these aspects contribute to an improved quality of life (QoL) of these patients. Moreover, when our trial was designed, no single agent or combination had as yet demonstrated a clear superiority over carboplatin alone, in any randomized trial.

The combination of carboplatin and paclitaxel is nowadays considered as the standard front-line therapy for advanced ovarian cancer. This regimen has also been studied as second-line therapy for platinum-sensitive relapsed patients. Two phase II trials and three retrospective studies have shown a significant response rate of 70% to 100% and a progression-free survival of 9–13 months [6–10]. Moreover, this combination was shown to be active in patients who had previously been treated with paclitaxel and platinum as first-line therapy. In addition, in a recently reported large phase III trial, the ICON/AGO investigators demonstrated the superiority of paclitaxel and platinum-based combination over a conventional platinum-based chemotherapy in platinum-sensitive patients [11].

To assess whether the combination of paclitaxel–carboplatin is more active than carboplatin alone in platinum-sensitive relapsed ovarian carcinoma, we performed a randomized phase II trial, the results of which are the basis of this report.

## Materials and methods

### Patients' eligibility criteria

Patients participating in the Grupo Español de Investigación en Cáncer de Ovario (GEICO) 0199 trial were required to meet the following eligibility criteria: recurrent, histologically confirmed epithelial ovarian cancer; platinum-sensitive disease, defined as tumor progression >6 months following the completion of platinum-based chemotherapy; no more than two previous chemotherapy lines; the last regimen administered must have included a platinum-derived compound; bidimensionally measurable disease as measured by computed tomography (CT) scan, or clinically evident but non-measurable disease that was evaluable by CA-125 Rustin's criteria; Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and a life expectancy of at least 12 weeks; adequate bone marrow (granulocytes $\geq 2000/mm^3$, platelets $\geq 100\,000/mm^3$), renal (creatinine clearance ≥40 ml/min) and liver (serum bilirubin and transaminases <1.5× upper normal limit) function; age >18 years; and written informed consent provided.

The protocol was approved by the Agencia Española del Medicamento (Spanish Drug Agency), as well as by the local ethics committee of each participating institution.

### Pretreatment evaluation

Baseline examinations included a complete history and physical examination with documentation of all measurable disease. Further analyses included: a complete blood count, blood chemistry analyses including liver and renal function test, ovarian tumor marker CA-125, electrolytes, urinalysis, chest X-ray, electrocardiogram and a CT scan to document measurable disease.

### Treatment

Patients were randomized to either single-agent carboplatin area under the curve (AUC) 5 (arm A) or paclitaxel 175 mg/m$^2$ over 3 h + carboplatin AUC 5 (arm B). Both treatments were administered every 3 weeks for a minimum of six cycles unless there was progression, unacceptable toxicity or patient refusal. After six courses the patients could continue therapy for three further cycles if, in the opinion of the attending physician, further clinical benefit could be expected.

The carboplatin dose was determined by the AUC method of Calvert [dose in mg = AUC × (GFR + 25]. The AUC chosen was 5 in both arms. The glomerular filtration rate (GFR) was calculated by the Cockcroft–Gault formula. Carboplatin was diluted in 250 ml of 5% dextrose and infused over a period of 30–60 min.

Patients assigned to arm B received paclitaxel 175 mg/m$^2$ infused over 3 h before carboplatin administration. All patients were treated with standard premedication of dexamethasone, dyphenhydramine and ranitidine ∼30 min before the administration of paclitaxel.

Treatment was repeated on a 21-day schedule if blood counts recovered (neutrophils $\geq 1500/mm^3$ and platelets $\geq 100\,000/mm^3$) and non-hematological toxicity recovered to grade ≤1. A delay of more than 42 days in any one course of treatment administration was sufficient to have the patient transferred out of the study.

### Dose modifications

Patients with neutropenic fever, grade 4 neutropenia lasting >7 days or grade 4 thrombocytopenia could continue treatment with a dose reduction of carboplatin to AUC 4 in arm A and to carboplatin AUC 4 + paclitaxel 150 mg/m$^2$ in arm B.

Paclitaxel was reduced to 135 mg/m$^2$ in case of grade 2 peripheral neurotoxicity, or grade 3 mucositis.

When dose reduction was required, no subsequent dose escalation was allowed.

Patients with cardiac arrhythmia or grade 3 hypersensitivity reaction were withdrawn from the study.

### Evaluation of response, toxicity and time-related parameters

All patients who received at least the first dose were evaluated for toxicity and response. All toxicities encountered during the study were evaluated according to the National Cancer Institute Common Toxicity Criteria.

Evaluation during the study included: (i) before each course of therapy: a history and physical examination, a complete blood count, differential count, platelet count, blood chemistry survey with renal and liver function tests, and evaluation of measurable disease by physical examination; (ii) CA-125 was measured following every two courses; and (iii) appropriate imaging studies were performed to assess measurable disease every three cycles. WHO response criteria were employed for evaluation of measurable disease.

In those patients without measurable disease, response was determined according to CA-125 Rustin's criteria [12].

Overall survival was measured from the date of randomization to the date of death. Time to progression was defined as the time from date of randomization to date of documentation of tumor progression.

QoL was assessed by the validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30). The QLQ-C30 should be filled out before study entry, every two cycles, and 6 and 12 months after the last treatment.

### Criteria for withdrawal from the study

Patients were removed from the study for any one of the following reasons: (i) evidence of disease progression after a minimum of one cycle

of therapy; (ii) development of unacceptable toxicity; or (iii) patient refusal or inability to comply with protocol requirements.

### Statistical analyses

This is a randomized phase II trial in which patients meeting all the inclusion criteria were randomized by a central data center. Eligible patients were blocked by platinum-free interval (6–12 months versus >12 months) and the number of previous chemotherapy lines (one versus two).

The primary end point of our study was objective response [complete (CR) plus partial response (PR)]. Secondary end points were toxicity, QoL, time to progression (TTP) and overall survival (OS). The response rate was calculated on all randomized patients following the intention-to-treat principle. A corresponding 95% confidence interval (95% CI) for the response rate was estimated. Survival rates and TTP were described using the Kaplan–Meier method.

This study was a 'pick up the winner' design based on the randomized phase II clinical trials approach proposed by Simon et al. [13], which gives a 90% chance of selecting the better treatment if the difference is at least 15% and the smaller response rate is assumed to be 30%. Although no formal statistical comparison between the two arms was planned, Fisher's exact test was performed on the response rate and toxicity levels, while the log-rank test was applied to the survival curves. These tests were for exploratory purposes only, and all expressed $P$ values are two-sided.

## Results

### Patients' characteristics

Between May 2000 and December 2002, 81 patients were randomized for entry into the study: 41 patients to the paclitaxel–carboplatin arm and 40 patients to the carboplatin arm. Three patients randomized to the combination arm did not receive a single cycle, one owing to a rapid clinical worsening due to intestinal obstruction and two because consent was withheld. These patients were included in the intention-to-treat analysis for response but were excluded from all other statistical evaluations. As such, the data from 78 treated patients are presented and their characteristics are summarized in Table 1. Median age was 61 years in the carboplatin arm (range 35–77) and 59 years in the combination arm (range 40–77). The majority of patients (84.6%) had received only one previous line of chemotherapy and the platinum-free interval was >12 months in 57.7% of patients. Most of the patients (87.2%) had received paclitaxel previously and 83.3% of the patients had received it as the chemotherapy prior to the present trial. More patients with ECOG performance status 2 were included in the carboplatin arm, but this difference was not statistically significant. Although two or more tumor locations and tumor size >5 cm were more frequent in the paclitaxel–carboplatin arm, there were no statistically significant differences in these and other important prognostic factors at the time of relapse. Overall, two-thirds of patients had measurable disease and one-third were evaluated by CA-125 criteria. The median platinum-free interval was almost identical in both arms: 14 months in the carboplatin arm (range 6–60) and 13.5 months in the combination arm (range 7–147).

### Treatment delivery

A total of 419 cycles were administered; 212 to the 40 patients treated with carboplatin and 207 to the 38 patients treated with paclitaxel–carboplatin. The median number of cycles administered was six in both arms (range two to nine in arm A, and one to eight in arm B). Dose reduction was uncommon, ocurring in 4.7% of cycles in arm A and 6.6% of cycles in arm B. However, dose delay was significantly more frequent in the monotherapy arm (34.4% versus 21% of the cycles in arm A versus arm B, respectively; $P = 0.006$). The main reason for delay was absence of hematological recovery (granulocytes or platelets) by day 21.

### Toxicity

There were 78 patients who received at least one cycle of treatment and were evaluable for the analysis of safety of treatment. Severe neutropenia (grade 3–4) was more common in the paclitaxel–carboplatin arm at 18.4% of patients, compared with 10% in the carboplatin arm ($P = 0.24$). Conversely, grade 3–4 thrombocytopenia and anemia were more frequent in the carboplatin arm; 12.5% versus 2.6% and 15% versus 5.3%, respectively. However, these differences were not statistically significant. Four patients were transferred out of the study owing to delay in hematological recovery, two in arm A (prolonged thrombocytopenia and prolonged neutropenia) and two in arm B (prolonged neutropenia and prolonged thrombocytopenia). One patient in arm A and two patients in arm B had one febrile neutropenia episode each. No toxic deaths were observed.

Significant (grade 2–4) non-hematological toxicity was more commonly associated with the paclitaxel–carboplatin combination. Only one patient had a grade 4 event, consisting of anaphylaxis related to the carboplatin infusion, but this was resolved immediately with standard medication. The more relevant toxicities observed in arm B were: grade 2–3 mucositis in 18.4% of patients, grade 2–3 myalgia/arthralgia in 36.8% of patients and peripheral neurosensory toxicity in 23.7% of patients. All these toxicities were statistically significantly more frequent in arm B than in arm A. All patients with peripheral neuropathy had grade 2 toxicity, and no grade 3–4 was observed.

Other toxicities of note were nausea and vomiting, asthenia and anorexia. All were of mild to moderate intensity, and similar in both treatment arms.

There were 10 patients (12.8%) in whom there was some form of grade 2–4 carboplatin-related hypersensitivity reaction (four in arm A and six in arm B), and which was the reason for withdrawal from the study in seven patients (two in arm A and five in arm B). Tables 2 and 3 summarize the toxicity data.

### Efficacy

We observed eight CRs and 12 PRs in the 40 patients on arm A, for a total response rate of 50% (95% CI 33.8% to 66.2%).

**Table 1.** Patient characteristics

| Characteristic | Patients [*n*(%)] | Carboplatin (*n* = 40) [*n*(%)] | Carboplatin+paclitaxel (*n* = 38) [*n*(%)] |
|---|---|---|---|
| Age, years [median (range)] | 60 (35–77) | 61 (35–77) | 59 (40–77) |
| ECOG performance status | | | |
| 0 | 31 (41.3) | 14 (35.9) | 17 (47.2) |
| 1 | 35 (46.7) | 18 (46.2) | 17 (47.2) |
| 2 | 9 (12.0) | 7 (17.9) | 2 (5.6) |
| Not reported | 3 | 1 | 2 |
| Histology subtype | | | |
| Serous | 56 (67.5) | 27 (67.5) | 29 (76.3) |
| Mucinous | 2 (2.6) | – | 2 (5.3) |
| Endometrioid | 4 (5.1) | 2 (5.0) | 2 (5.3) |
| Clear cell | 7 (9.0) | 5 (12.5) | 2 (5.3) |
| Undifferentiated | 6 (7.7) | 5 (12.5) | 1(2.6) |
| Other | 3 (3.8) | 1 (2.5) | 2 (5.3) |
| Poorly differentiated grade | 36 (51.4) | 20 (54.1) | 16 (48.5) |
| TFI, months | | | |
| Median (range) | 14 (6–147) | 14 (6–60) | 13.5(7–147) |
| 6–12 months | 33 (42.3) | 16 (40.0) | 17 (44.7) |
| >12 months | 45 (57.7) | 24 (60.0) | 21 (55.3) |
| Prior chemotherapy | | | |
| One regimen | 66 (84.6) | 35 (87.5) | 31 (81.6) |
| Two regimens | 12 (15.6) | 5 (12.5) | 7 (18.4) |
| Previous paclitaxel | | | |
| In any regimen | 68 (87.2) | 33 (82.5) | 35 (92.1) |
| In last regimen | 65 (83.3) | 33 (82.5) | 32 (84.2) |
| No. of involved sites | | | |
| 1–2 | 58 (74.4) | 33 (82.5) | 25 (65.8) |
| >2 | 20 (25.7) | 7 (17.5) | 13 (34.2) |
| Tumor size >5 cm | 13 (16.7) | 5 (12.5) | 8 (21.1) |
| Response assessment | | | |
| WHO criteria | 52 (66.6) | 25 (62.5) | 27 (71) |
| CA-125 criteria | 26 (33.3) | 15 (37.5) | 11 (28.9) |

ECOG, Eastern Cooperative Oncology Group; TFI, treatment-free interval.

**Table 2.** Hematological toxicity

| Toxicity | Carboplatin (*n* = 40) [*n* (%)] | | | | | | Carboplatin + paclitaxel (*n* = 38) [*n* (%)] | | | | | | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NCI CTC grade | | | | | | NCI CTC grade | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 3 + 4 | 0 | 1 | 2 | 3 | 4 | 3 + 4 | |
| Leukopenia | 17 | 16 | 6 | 1 | – | 1 (2.5) | 19 | 11 | 6 | 2 | – | 2 (5.3) | 0.93 |
| Neutropenia | 13 | 11 | 12 | 3 | 1 | 4 (10.0) | 16 | 7 | 8 | 6 | 1 | 7 (18.4) | 0.24 |
| Thrombocytopenia | 8 | 17 | 10 | 3 | 2 | 5 (12.5) | 20 | 12 | 5 | 1 | – | 1 (2.6) | 0.25 |
| Anemia | 4 | 20 | 10 | 5 | 1 | 6 (15.0) | 8 | 20 | 8 | 2 | – | 2 (5.3) | 0.33 |

NCI CTC, National Cancer Institute Common Toxicity Criteria.

**Table 3.** Non-hematological toxicity

| Toxicity | Carboplatin ($n=40$) [$n$(%)] | | | | | | Carboplatin + paclitaxel ($n=38$) [$n$(%)] | | | | | | $P$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NCI CTC grade | | | | | | NCI CTC grade | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 2+3+4 | 0 | 1 | 2 | 3 | 4 | 2+3+4 | |
| Allergy | 33 | 4 | 3 | 1 | – | 4 (10) | 28 | 4 | 2 | 3 | 1 | 6 (15.8) | |
| Alopecia | 30 | 3 | 7 | – | – | 7 (17.5) | 5 | – | 11 | 22 | – | 33 (86.8) | 0.001 |
| Fever | 36 | 4 | – | – | – | – | 34 | 2 | 2 | – | – | 2 (5.3) | |
| Infection | 39 | – | – | 1 | – | 1 (2.5) | 33 | 3 | 1 | 1 | – | 2 (5.3) | |
| Hemorrhage | 36 | 4 | – | – | – | – | 36 | 2 | – | – | – | – | |
| Nausea | 13 | 15 | 12 | – | – | 12 (30.0) | 17 | 15 | 6 | – | – | 6 (15.8) | |
| Vomiting | 21 | 9 | 6 | 4 | – | 10 (25.0) | 24 | 9 | 4 | 1 | – | 5 (13.2) | |
| Stomatitis/mucositis | 37 | 3 | – | – | – | – | 27 | 4 | 7 | – | – | 7 (18.4) | 0.004 |
| Diarrhea | 34 | 5 | 1 | – | – | 1 (2.5) | 35 | 2 | 1 | – | – | 1 (2.6) | |
| Constipation | 27 | 10 | 3 | – | – | 3 (7.5) | 25 | 10 | 3 | – | – | 3 (7.9) | |
| Creatinine | 35 | 4 | 1 | – | – | 1 (2.5) | 36 | 1 | 1 | – | – | 1 (2.6) | |
| Pulmonary (dyspnea) | 38 | 1 | 1 | – | – | 1 (2.5) | 35 | 1 | 1 | 1 | – | 2 (5.3) | |
| Neurosensory | 34 | 6 | – | – | – | – | 17 | 12 | 9 | – | – | 9 (23.7) | 0.009 |
| Myalgias/arthralgias | 39 | 1 | – | – | – | – | 15 | 9 | 12 | 2 | – | 14 (36.8) | 0.001 |
| Mood depression | 39 | – | 1 | – | – | 1 (2.5) | 36 | 1 | – | 1 | – | 1 (2.6) | |
| Asthenia | 20 | 10 | 10 | – | – | 10 (25.0) | 16 | 11 | 9 | 2 | – | 11 (28.9) | |
| Anorexia | 35 | 1 | 3 | 1 | – | 4 (10.0) | 35 | 2 | 1 | – | – | 1 (2.6) | |

NCI CTC, National Cancer Institute Common Toxicity Criteria.

There were 11 CRs and 20 PRs in the 38 patients in arm B; a response rate of 81.5% (95% CI 65.7% to 92.3%). According to our study design, arm B was chosen as the 'winner' (see Statistical analyses section). For exploratory purposes, a comparison between both response rates was carried out, showing a statistically significant difference in favor of arm B ($P=0.003$). This difference was still significant in the intention-to-treat analysis, which included the three patients randomized to arm B but who did not receive any cycle of chemotherapy. The response rate in arm A was 50% (95% CI 33.8% to 66.2%) compared with 75.6% in arm B (95% CI 59.7% to 87.6%) ($P=0.017$). The rate of progression was significantly higher in the carboplatin alone arm (32.5% versus 4.9%; $P=0.001$). Responses to treatment are summarized in Table 4.

The median TTP for patients in arm A was 33.7 weeks (95% CI 25.8–41.5), and in arm B was 49.1 weeks (95% CI 36.9–61.3). This difference was statistically significant in an exploratory comparison [hazard ratio (HR) 0.54; 95% CI 0.32–0.92; $P=0.021$ on the log-rank test] (Figure 1). With a median follow-up of 67.7 weeks, 23 patients on arm A and nine on arm B have died. Median OS has not been reached with paclitaxel and carboplatin, being significantly better than the 72.7 weeks (95% CI 53.8–91.6) obtained with carboplatin alone (HR 0.31; 95% CI 0.14–0.68; $P=0.0021$ on the log-rank test) (Figure 2).

**Table 4.** Response to therapy (all patients included)

| Response category | Carboplatin ($n=40$) | | Carboplatin + paclitaxel ($n=41$) | | $P$ |
|---|---|---|---|---|---|
| | $n$ | % (95% CI) | $n$ | % (95% CI) | |
| Complete response | 8 | 20 (9.1–35.6) | 11 | 26.8 (14.2–42.9) | |
| Partial response | 12 | 30 (16.6–46.5) | 20 | 48.8 (32.9–64.9) | |
| Overall response | 20 | 50 (33.8–66.2) | 31 | 75.6 (59.7–87.6) | 0.017 |
| Stable disease | 5 | 12.5 (4.2–26.8) | 2 | 4.9 (0.6–16.5) | |
| Progression | 13 | 32.5 (18.6–49.0) | 2 | 4.9 (0.6–16.5) | 0.001 |
| Not assessable | 2 | 5.0 (0.6–16.9) | 6 | 14.6 (5.6–29.2) | |

CI, confidence interval.

## Quality of life

Compliance with the protocol requirements was high during therapy, with a rate of non-returned questionnaires of 14.1% at baseline, 18.7% after cycle 2, 19% after cycle 4 and 21.4% after cycle 6. However, these figures increased dramatically at 6 months follow-up, to 86.8%, and to 94.6% at 12 months follow-up.

No significant differences were observed during therapy in any of the five function scales of the QLQ-C30 questionnaire; physical (PF), role (RF), emotional (EF), cognitive (CF) and social (SF). There were no differences in the two symptom scales of fatigue (FA) and pain (PA), nor on the six single-item

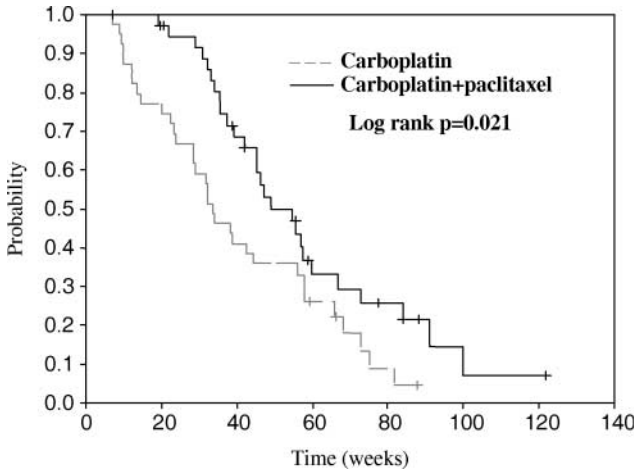


**Figure 1.** Time to progression

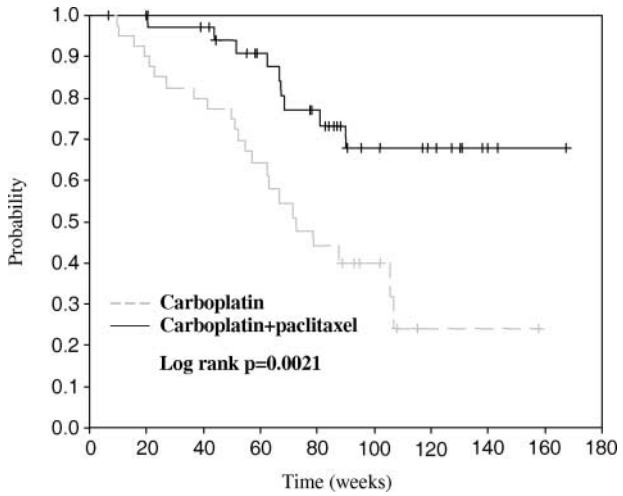


**Figure 2.** Overall survival

scales of dyspnea (DY), sleep disturbance (SL), appetite loss (AP), constipation (CO), diarrhea (DI) and financial impact of the disease/treatment (FI). The overall health status/QoL status was not statistically different between the two treatment arms. Only nausea and vomiting (NV) was higher in the carboplatin monotherapy arm ($P = 0.033$). A trend towards a better overall QoL was observed in both arms between cycles 2 and 6.

## Discussion

The treatment of patients with platinum-sensitive recurrent ovarian cancer has been influenced by the fact that it is an incurable disease and, as such, palliation is the principal objective. With this concept in mind, monotherapy has been chosen as the standard option by the majority. Carboplatin alone has been the usual choice based on its ease of administration, low toxicity profile and activity [4, 5].

The results of the present study show that the combination of paclitaxel (175 mg/m$^2$) combined with carboplatin (at AUC 5) achieves a significantly higher response rate compared with carboplatin alone in patients with ovarian carcinoma recurring >6 months after a platinum-based treatment regimen. The response rate observed in the combination arm of our study is similar to those observed in phase II trials with paclitaxel–carboplatin combination in platinum-sensitive patients [6–10]. Conversely, the response rate obtained with carboplatin alone is comparable to data derived from studies recently reported involving retrospective analyses in patients with platinum-sensitive relapse following paclitaxel–platinum first-line therapy [5].

Although, the present study was not designed and powered to detect differences in survival, the exploratory analysis of TTP and OS showed a significant superiority of the paclitaxel–carboplatin combination over the single-agent carboplatin in both survival end points.

The results of this trial are consistent with those recently published by the ICON/AGO investigators [11]. The ICON-4/AGO-OVAR 2.2 trial is the largest trial communicated to date in platinum-sensitive, relapsed ovarian carcinoma. The trial involves a total of 802 patients randomized to a platinum regimen without paclitaxel or the combination of paclitaxel with a platinum-derived salt. The majority of patients received carboplatin alone in the control arm (71%). With a median follow-up of 42 months, the combination arm achieved a significantly higher progression-free survival (9 versus 12 months) and OS (24 versus 29 months).

In addition, the recently reported result of the adequately powered AGO-2.5 trial showing a significant better response rate and progression-free survival of carboplatin and gemcitabine combination over carboplatin alone, adds to the evidence of the superiority of platinum-based combination chemotherapy over platinum-based monotherapy [14].

If we compare the patient characteristics of both studies (ICON-4 and GEICO-0199), the populations are very similar. For example, the majority received only one prior line of chemotherapy (90% in ICON-4 and 84.6% in GEICO-0199). However, there are some notable differences, such as more patients with a platinum-free interval >12 months in the ICON study compared with the GEICO (75% versus 57.7%, respectively).

One point of contention in the ICON/AGO study is that only 40% of patients had received paclitaxel previously, which could explain the superiority of the paclitaxel arm following the relapse [15]. In our study, 87.2% of patients had received paclitaxel previously and in 83.3% this treatment was part of the last one prior to the present trial. The results suggest that the combination of paclitaxel and carboplatin is still active in patients with relapse several months after the initial paclitaxel–platinum combination was administered as first-line therapy.

Another issue worth noting is the influence on survival of treatment following disease progression with the carboplatin regimen. The results from the GOG-132 trial suggested that sequential administration of cisplatin and paclitaxel could achieve the same outcome as the combination therapy used as first-line treatment [16]. In our study, only five patients treated

with carboplatin alone had received paclitaxel as further therapy following disease progression. As such, we cannot rule out the possibility that sequential administration of paclitaxel following carboplatin therapy could have reduced the differences observed with respect to survival. However, the re-introduction of paclitaxel in relapse is not as widely accepted as the re-introduction of a platinum in those patients with a platinum-free interval over 6 months. Actually, more than 50% of patients in both arms received further active drugs (such as pegylated liposomal doxorubicin or topotecan) at progression. Moreover, this study was not designed to determine whether carboplatin and paclitaxel should be given concurrently or sequentially at platinum-sensitive relapse, since the principal objective of our trial was to assess whether the combination of paclitaxel–carboplatin was more active than carboplatin alone in platinum-sensitive relapsed ovarian carcinoma.

The analysis of safety shows that both treatments are well tolerated. However, non-hematological toxicity was higher in the paclitaxel–carboplatin arm, with clinically significant (grade 2–3) mucositis (18.4% of patients), alopecia (86.8%) myalgia/arthralgia (36.8%) and peripheral neurosensory toxicity (23.7%) as the most relevant adverse events. It should be noted that the rate of grade 2–4 peripheral neurotoxicity is similar to the 20% reported by the ICON/AGO investigators, but with our patient population having a higher prior exposure to paclitaxel than those in the ICON/AGO trial. In addition, no grade 3–4 peripheral neuropathy was observed. Despite these differences in toxicity, the QoL analysis during therapy did not show significant differences between the two treatment arms, except for more nausea and vomiting in the monotherapy arm. Clearly no deteriorating toxicity influenced QoL in patients allocated to the combination therapy. On the other hand, our QoL assessment method may not have been sensitive enough to discriminate relevant differences among arms, and this could explain why a better response rate and TTP did not translate into better QoL.

In summary, despite the limitations of a randomized phase II study, our results add to the evidence from ICON-4/AGO OVAR 2.2 trials indicating a benefit of paclitaxel–carboplatin over carboplatin monotherapy. Therefore, patients with ovarian carcinoma relapsing after 6 months of first line paclitaxel–platinum should be treated again with the same combination if no significant residual neuropathy is present. This is particularly appropriate for those patients with relapses occurring >12 months after therapy. Whether carboplatin followed by paclitaxel would obtain the same outcome in this situation is an hypothesis that should be confirmed in a randomized clinical trial.

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